Docket No.: 000166.0108-US01
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
J. Michael Ramstack et al.

Application No.: 10/022,859 | Confirmation No.: 1415

Filed: December 20, 2001 | Art Unit: 1615

For: PREPARATION OF MICROPARTICLES HAVING IMPROVED FLOWABILITY | Examiner: S. L. Howard

APPEAL BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

As required under § 41.37(a), this brief is filed within two months of the Notice of Appeal filed in this case on June 21, 2005, and is in furtherance of said Notice of Appeal.

The fees required under § 41.20(b)(2) are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF. It is not believed that additional fees or extensions of time are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional fees or extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including additional fees required for this appeal) are hereby authorized to be charged to our Deposit Account No. 50-0740.

This brief contains items under the following headings as required by 37 C.F.R. § 41.37 and M.P.E.P. § 1206:

I. Real Party In Interest
II Related Appeals, Interferences, and Judicial Proceedings
III. Status of Claims
IV. Status of Amendments

I. REAL PARTY IN INTEREST

The real party in interest for this appeal is:

Alkermes Controlled Therapeutics Inc. II (assignee of the present application).

II. RELATED APPEALS, INTERFERENCES, AND JUDICIAL PROCEEDINGS

There are no other appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are forty-six (46) claims pending in the above-captioned application. Claims 65, 80, 94, 103, 107, 108, 109, 114, 116, and 117 are the independent claims.

B. Current Status of Claims

1. Claims canceled: 1-64; 91-93; and 100
2. Claims withdrawn from consideration but not canceled: None
3. Claims pending: 65-90; 94-99; and 101-118
4. Claims allowed: None
5. Claims rejected: 65-90; 94-99, and 101-118

C. Claims On Appeal

The claims on appeal are claims 65-90, 94-99, and 101-118.

IV. STATUS OF AMENDMENTS

Applicant did not file an Amendment After Final Rejection. An Amendment in Response to Non-Final Office Action was filed by Applicant on March 31, 2004. A Final Rejection issued nearly a year later, on March 21, 2005. A Notice of Appeal and Request for Oral Hearing were filed on June 21, 2005 in response to the Final Rejection.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention provides a method to improve flowability of a microparticle product. "Microparticles" or "microspheres" refer to solid particles that include a polymer that serves as a matrix or binder of the particle. (Appl. No. 10/022,859 (hereinafter "the '859 application"), page 9, lines 1-3.) The flowability of the microparticle product is improved by the present invention to allow processing in conventional hoppers and automated vial filling equipment. The characteristics and importance of flowability are explained on page 3, lines 12-21 of the '859 application:

> Good flowability is characterized by steady, controlled flow similar to dry sand. Poor flowability, on the other hand is characterized by uncontrolled, erratic flow similar to wet sand. In this case the entire bulk tries to move in a solid mass. This last condition is termed "floodable" flow and is most characteristic of cohesive, sticky powders. Flowability is an important consideration in large-scale processing when invariably these powders or microparticles must be moved from place to place. It is a particularly important consideration when using automated filling equipment where material must flow from a hopper. Microparticles having poor flow properties tend to "arch" or "bridge" and then may "rat hole" or stop completely when discharged from the hopper. In this case further processing must be abandoned.

The present invention provides a method by which the flowability of the microparticle product is improved to allow processing in conventional hoppers and automated vial filling equipment. Poor flowability often results from conventional formulation and processing techniques for microparticles. By solving the poor flowability problem as a final

processing step, the present invention advantageously avoids reformulation or redesign of established formulations, processes, and equipment.

The '859 application describes a number of properties that can be used to characterize flowability. One such property is the "angle of repose." As explained on page 7, line 20 through page 8, line 2, "angle of repose" refers to the limiting angle of incline, θ_r, at which a body on the incline will remain at rest. With respect to the present invention, the angle of repose can be considered as the constant angle to the horizontal assumed by a cone-like pile of microparticles. As explained at page 11, line 24, through page 12, line 11 of the '859 application, the angle of repose can be measured by allowing microparticles to flow out of a funnel until all material is discharged. The discharged microparticles form a pile having an angle of repose characteristic of the microparticles forming the pile. A pile **100** of microparticles is depicted in FIG. 1. The height of the pile (h), the diameter of the pile (d), and the width (w) where the height of the pile was measured, are all recorded. The angle of repose is calculated from the recorded dimensions using the formula:

$$\theta_r = \tan^{-1} \{\text{height (h)/width (w)}\}.$$

θ_r is the angle of incline at which the microparticles forming pile **100** remain at rest. As shown in Tables 1 and 2 of the '859 application, microparticles that are poor flowing have a higher angle of repose (*i.e.*, form a taller pile with greater height (h)) than microparticles that have greater flowability. Conversely, microparticles with improved flowability have a lower angle of repose (*i.e.*, form a shorter and wider pile with lower height (h)) than microparticles having poorer flowability. Tables 1 and 2 show the angle of repose and flow property as a function of the conditioning process of the present invention. With no conditioning (represented by "None" in Table 1 and zero days in Table 2), the flowability of the microparticles was "poor," and the angle of repose was greater than about 37°. The conditioning process of the present invention improved the flowability to "good" or "excellent," all of which are characterized by an angle of repose of less than 28°.

As explained on page 20, line 8 through page 23, line 2 of the '859 application, another property that can be used to characterize flowability is the "flowability index." As shown in Table 6 and explained in the accompanying text on page 21, the flowability index is

derived by measuring four parameters, converting each of the measured values into a point score, and summing the four point scores. The four parameters, known as the "Carr Parameters," are as follows: (i) angle of repose; (ii) compressibility; (iii) angle of spatula; and (iv) cohesion. Table 7 shows the affect on the flowability index of the conditioning process of the present invention. The flowability index was found to be a good prediction of bulk material flow, and acceptable microparticle flowability occurred when the flowability index was greater than about 60. As shown in Table 7, all of the conditioned microparticles had a flowability index greater than about 60, and an angle of repose less than about 37°.

The conditioning process of the present invention is carried out on a finished microparticle product, such as a batch or quantity of microparticles prepared by, for example, the process disclosed and described in U.S. Patent Nos. 5,654,008 and 5,650,173. As explained on page 10 of the '859 application, a batch of microparticles is preferably conditioned by maintaining the batch at a conditioning temperature for a period of time. The conditioning temperature and the period of time are selected to achieve a measured flowability characteristic that corresponds to improved flowability. In particular, the conditioning temperature and the period are selected so that a flowability index of the batch of microparticles is greater than about 60. Alternatively, the conditioning temperature and the period are adjusted so that the angle of repose of the microparticles is less than about 28°. As explained on pages 18-19 of the '859 application, the conditioning process serves to harden the surfaces of the microparticles, and, by hardening the microparticles, flowability was improved. As shown in Table 5 on page 19 of the '859 application, microparticles having a hardness greater than about 0.4 Mpa exhibited the best flowability.

To ensure sterility and stability of the microparticles, the conditioning process is carried out in a closed container with a dry product. It may be carried out in a completely closed container that is placed in a controlled-temperature chamber. The temperature in the chamber, and the length of time the container is in the chamber, are both controlled. Processing the material in a closed container preserves the sterility of the microparticle product, avoids yield losses and contamination associated with handling and product transfers, and minimizes moisture pick-up by avoiding atmospheric contact.

Independent claims 65 and 80 are directed to improving the flowability of microparticles by conditioning the microparticles and measuring the flowability index of the conditioned microparticles. If the flowability index of the conditioned microparticles is not greater than about 60, then the conditioning is repeated until the flowability index is greater than about 60. Independent claim 94 is directed to a similar process whereby a hardening step is carried out to form hardened microparticles, and the flowability index of the hardened microparticles is measured. If the flowability index of the hardened microparticles is not greater than about 60, then the hardening step is repeated until the flowability index is greater than about 60.

Independent claims 103 and 109 are directed to improving the flowability of microparticles by selecting a conditioning temperature and a time period for processing the microparticles, maintaining the microparticles at the conditioning temperature for the time period, and measuring the angle of repose. If the angle of repose of the microparticles is not less than about 28°, then the conditioning temperature and the time period are adjusted so that the angle of repose of the microparticles is less than about 28°. Independent claim 116 is directed to a similar process using a flowability index. A conditioning temperature and a time period for processing the microparticles is selected, the microparticles are maintained at the conditioning temperature for the time period, and a flowability index of the microparticles is measured. If the flowability index is not greater than about 60, then the conditioning temperature and the time period are adjusted so that the flowability index of the microparticles is greater than about 60.

Independent claims 107 and 108 are directed to improving the flowability of microparticles by maintaining the microparticles at a conditioning temperature for a time period. The conditioning temperature and the time period are determined by: (i) maintaining a portion of the microparticles at the conditioning temperature for the time period; (ii) measuring an angle of repose of the microparticles; and (iii) if the angle of repose of the microparticles is not less than about 28°, adjusting the conditioning temperature and the time period and repeating steps (i) and (ii) until the angle of repose of the microparticles is less than about 28°.

Independent claim 114 is directed to a method for processing microparticles to improve flowability that includes determining a conditioning temperature and a time period for

processing the microparticles, and maintaining the microparticles at the conditioning temperature for the time period, with the angle of repose of the microparticles being less than about 28° at the completion of the maintaining step.[1]

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

All pending claims, 65-90, 94-99, and 101-118 stand finally rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,653,173 ("the Ramstack patent"). On page 3 of the Final Office Action, the Examiner states "Ramstack *et al.* [the Ramstack patent] do not specifically teach that the microparticles are 'maintained' at 'a certain temperature' for a 'certain period of time.' However, it is the position of the examiner that the cited reference still renders applicant's claimed process obvious." To provide the critical support needed for this rejection, the Examiner asserts that "it is within the ordinary skill of the pharmaceutical art to set aside a recently made batch of microparticles, allowing them to thoroughly dry, prior to using the microparticles in any further formulations. Additionally, it is within the knowledge of the ordinary artisan that increased dryness equals increased flowability."

Claims 65-86, 88-90, 94-99, 101-111 and 113-118 also stand finally rejected under 35 U.S.C. § 103(a) as being unpatentable over "Use of polylactic acid for the preparation of microparticulate drug delivery systems by Conti *et al.* ("the Conti article"). The Examiner's reasoning for the Conti article is substantially the same as described above for the Ramstack patent. The Examiner notes the same lack of teaching in the Conti article of the maintaining and conditioning steps of the present invention, and the Examiner makes the same assertions regarding setting aside microparticles to allow them to thoroughly dry, and that increased dryness equals increased flowability.

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[1] The '859 application is a continuation-in-part of Appl. No. 09/748,136, filed December 27, 2000 ("the parent application"; now abandoned in favor of the '859 application). An Examiner interview was held on August 6, 2002 in the parent application with Examiner Pulliam, who is also the Examiner for the '859 application, and Primary Examiner Kishore. In discussing the claims of the parent application, Primary Examiner Kishore suggested that the claims be amended to recite: (a) the purpose of the processing of the microparticles (*i.e.*, to improve flowability); (b) an affirmative step of measuring or determining the flowability characteristic (*e.g.*, angle of repose or flowability index); and (c) the polymer material for the microparticles. All of these suggestions have been incorporated into each of the appealed independent claims. Primary Examiner Kishore also recommended including an upper limit on the time period for the conditioning. Each of independent claims 103, 107, 108, 109, 114, 116, and 117 also include an upper limit on the time period for conditioning.

VII. ARGUMENT

A. REJECTION UNDER 35 U.S.C. § 103(a) BASED ON THE RAMSTACK PATENT

1. *Claims 65-90, 94-99, and 101-102*

Independent claims 65, 80, and 94 (and dependent claims 66-79, 81-90, 95-99, and 101-102) have all been rejected under 35 U.S.C. § 103(a) as being unpatentable over the Ramstack patent. As noted in Section VI above, on page 3 of the Final Office Action, the Examiner states "Ramstack *et al.* [the Ramstack patent] do not specifically teach that the microparticles are 'maintained' at 'a certain temperature' for a 'certain period of time.' However, it is the position of the examiner that the cited reference still renders applicant's claimed process obvious." To provide the critical support needed for this rejection, the Examiner asserts that "it is within the ordinary skill of the pharmaceutical art to set aside a recently made batch of microparticles, allowing them to thoroughly dry, prior to using the microparticles in any further formulations. Additionally, it is within the knowledge of the ordinary artisan that increased dryness equals increased flowability." Not only are the foregoing assertions made by the Examiner unsupported by any evidence, they are also contrary to the data presented in the '859 application and the explanation provided in the Declaration of J. Michael Ramstack, Ph.D. Under 37 C.F.R. § 1.132 filed on March 31, 2004 ("the Ramstack Declaration"; a copy of which is attached hereto as Appendix B; *see* Section IX below).

(1) The Unsupported Assertions and Request Under M.P.E.P. § 2144.03

The assertions and reasoning cited above from the Final Office Action were merely copied by the Examiner from the non-final Office Action dated December 1, 2003 (Paper No. 5). In responding to the December 1, 2003 Office Action, Applicant filed an amendment on March 31, 2004 that specifically challenged the assertions made by the Examiner under M.P.E.P. § 2144.03C, by which the Examiner is bound. As explained in M.P.E.P. § 2144.03, any facts noticed or asserted as within common knowledge should be "of notorious character and serve only to 'fill in the gaps' in an insubstantial manner which might exist in the evidentiary showing made by the examiner to support a particular ground for rejection." M.P.E.P. § 2144.03 E. To this date, the Examiner has never provided an evidentiary showing with respect to the conditioning and maintaining steps of the claims of the present invention, because, as recognized

by the Examiner, this subject matter is lacking in the Ramstack patent. The assertions made by the Examiner regarding setting aside microparticles to thoroughly dry, and that increased dryness equals increased flowability, are not insubstantial assertions made to fill in the gaps. Rather, these assertions are the foundations upon which the rejection is based. It is never appropriate to rely solely on common knowledge in the art without evidentiary support in the record as the principal evidence upon which a rejection is based. *In re Zurko*, 258 F.3d 1379, 1386 (Fed. Cir. 2001); M.P.E.P. § 2144.03.

Because the Examiner had not provided the requisite evidentiary showing in the December 1, 2003 Office Action, in the responsive amendment Applicant traversed under M.P.E.P. § 2144.03 C the following two assertions made by the Examiner, and requested that the Examiner provide documentary evidence in support of these assertions should the rejection be maintained in the next Office Action.

(1) It is within the ordinary skill of the pharmaceutical art to set aside a recently made batch of microparticles, allowing them to thoroughly dry, prior to using the microparticles in any further formulations.

(2) It is within the knowledge of the ordinary artisan that increased dryness equals increased flowability.

The next Office Action that issued is the Final Office Action from which this appeal is taken. In the Final Office Action, the Examiner provided no evidentiary support in response to the explicit request under M.P.E.P. § 2144.03 C. In fact, the Examiner made no mention at all of the request or argument made by Applicant under M.P.E.P. § 2144.03 C. The Examiner merely repeated the unsupported assertions from the non-final Office Action, and in the section entitled "Response to Arguments," summarily states that "[I]n response to applicant's arguments, the selection of a flowability index is within the skill of the art, and therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made."

Applicant respectfully submits that the Examiner has failed to establish a *prima facie* case of unpatentability based upon the Ramstack patent for at least the reason that the unsupported assertions form the principal evidence upon which the rejection is based. *Zurko*,

258 F.3d at 1386. The assertions made by the Examiner regarding setting aside microparticles to thoroughly dry, and that increased dryness equals increased flowability, are not insubstantial assertions made to fill in the gaps. Rather, these assertions are the foundations upon which the rejection is based. It is never appropriate to rely solely on common knowledge in the art without evidentiary support in the record as the principal evidence upon which a rejection is based. *Id.;* M.P.E.P. § 2144.03.

(2) The Ramstack Declaration

Not only are the two assertions made by the Examiner unsupported by any evidence, they are also contrary to the data presented in the '859 application and the explanation provided in the Ramstack Declaration. The Ramstack Declaration was filed on March 31, 2004, accompanying the amendment that traversed the rejection under M.P.E.P. § 2144.03.

Applicant submits that the Examiner's assertion that "increased dryness equals increased flowability" is contradicted by the data presented in the '859 application. As detailed in paragraph 3 of the Ramstack Declaration, the data presented for the Batch E microparticles (Table 3 on page 16 of the '859 application as originally filed) demonstrate that increased dryness can lead to decreased flowability. As detailed in paragraph 4 of the Ramstack Declaration, the data presented for the Batch F microparticles in Table 3 also demonstrate that increased dryness can lead to decreased flowability. Therefore, the Examiner's assertion that increased dryness equals increased flowability is refuted by the data presented in the '859 application itself.

The Examiner is taking the position that "set[ting] aside a recently made batch of microparticles, allowing them to thoroughly dry" is the same as the conditioning of the microparticles of the claimed invention. As noted in paragraph 4 of the Ramstack Declaration, such a position is refuted by the data presented in Table 3 for the Batch F microparticles. In particular, the Batch F microparticles demonstrate that conditioning the microparticles is not the same as drying the microparticles since the conditioned microparticles had better flowability than the microparticles after being further dried under vacuum. Moreover, as explained in paragraph 5 of the Ramstack Declaration, microparticles made using the methods disclosed in the Ramstack patent may exhibit poor flowability, even though the microparticles were thoroughly dried, and that the process of the present invention was discovered as a way to improve the flowability of dry but poorly flowing microparticles.

Paragraph 6 of the Ramstack Declaration makes clear that even if microparticles are allowed to thoroughly dry, that alone is not a guarantee of good flowability. Paragraph 6 of the Ramstack Declaration also makes clear that increased dryness cannot be equated with increased flowability, and that conditioning the microparticles cannot be equated with drying the microparticles.

The Examiner asserts on page 4 of the Final Office Action that "there has been no criticality placed on the length of time the microparticles are maintained at this temperature, or on the flowability index, or the angle of repose." Applicant submits that the above-captioned application is replete with discussions and data regarding the criticality of the angle of repose and the flowability index, and its relation to flowability. Such discussion can be found, for example, on pages 4, 5, 12-16, and 20-22 of the '859 application as originally filed.

On page 7 of the Final Office Action, the Examiner inexplicably takes the position that the Ramstack Declaration is insufficient to overcome the rejection "because the declaration does not support a scientific data that presents a comparison of the claimed particles and the particles of the Ramstack reference." The Examiner's reasoning is inapt and unavailing. The pending claims are all *method* claims - there are no claims directed to the microparticles themselves, nor are there any "product-by-process" claims. The Ramstack Declaration squarely addresses the rejection made by the Examiner, and unequivocally establishes that the Examiner has failed to make a *prima facie* case of unpatentability based upon the Ramstack patent (or the Conti article).

Applicant respectfully submits that the Examiner has failed to establish a *prima facie* case of unpatentability based upon the Ramstack patent for at least the additional reason that the unsupported assertions upon which the rejection is based are contrary to the data presented in the '859 application and the explanation provided in the Ramstack Declaration.

(3) Affirmative Step of Measuring

Each of independent claims 65 and 80 recite a step of "measuring a flowability index of the conditioned microparticles," and independent claim 94 recites a step of "measuring a flowability index of the hardened microparticles." None of the documents cited by the Examiner discloses or suggests the measuring steps contained in independent claims 65, 80, and 94.

Moreover, none of the documents cited by the Examiner discloses or suggests the claimed flowability index, and its relation to improving flowability of microparticles. For at least this reason as well, Applicant respectfully submits that the Examiner has failed to establish a *prima facie* case of unpatentability based upon the Ramstack patent.

2. *Claims 103-106, 109-113 and 116*

Independent claims 103, 109, and 116 (and dependent claims 104-106 and 110-113) have all been rejected under 35 U.S.C. § 103(a) as being unpatentable over the Ramstack patent on the same grounds and using the same rationale as detailed above in Section VII.A.1. for claims 65-90, 94-99, and 101-102. For all of the reasons discussed above in Section VII.A.1., which are incorporated here in their entirety by reference for brevity, Applicant submits that the Examiner has not established a *prima facie* case of unpatentability for claims 103-106, 109-113, and 116.

In particular, the Examiner has not established a *prima facie* case of unpatentability for claims 103-106, 109-113, and 116 for at least the following reasons. First, the Examiner has failed to establish a *prima facie* case of unpatentability based upon the Ramstack patent for at least the reason that the unsupported assertions form the principal evidence upon which the rejection is based. Second, the unsupported assertions upon which the rejection is based are contrary to the data presented in the '859 application and the explanation provided in the Ramstack Declaration. Third, each of independent claims 103 and 109 recites a step of "measuring an angle of repose of the microparticles," and independent claim 116 recites a step of "measuring a flowability index of the microparticles." None of the documents cited by the Examiner discloses or suggests the measuring steps contained in independent claims 103, 109, and 116. Moreover, none of the documents cited by the Examiner discloses or suggests the claimed angle of repose or flowability index, their relation to improving flowability of microparticles, and a time period of conditioning of less than about six days.

3. *Claims 107 and 108*

Independent claims 107 and 108 have both been rejected under 35 U.S.C. § 103(a) as being unpatentable over the Ramstack patent on the same grounds and using the same rationale

as detailed above in Section VII.A.1. for claims 65-90, 94-99, and 101-102. For all of the reasons discussed above in Section VII.A.1., which are incorporated here in their entirety by reference for brevity, Applicant submits that the Examiner has not established a *prima facie* case of unpatentability for claims 107 and 108.

In particular, the Examiner has not established a *prima facie* case of unpatentability for claims 107 and 108 for at least the following reasons. First, the Examiner has failed to establish a *prima facie* case of unpatentability based upon the Ramstack patent for at least the reason that the unsupported assertions form the principal evidence upon which the rejection is based. Second, the unsupported assertions upon which the rejection is based are contrary to the data presented in the '859 application and the explanation provided in the Ramstack Declaration. Third, each of independent claims 107 and 108 recites a step of "measuring an angle of repose of the microparticles." None of the documents cited by the Examiner discloses or suggests the measuring steps contained in independent claims 107 and 108. Moreover, none of the documents cited by the Examiner discloses or suggests the claimed angle of repose, its relation to improving flowability of microparticles, and a time period of conditioning of less than about six days.

4. *Claims 114 and 117*

Independent claims 114 and 117 have both been rejected under 35 U.S.C. § 103(a) as being unpatentable over the Ramstack patent on the same grounds and using the same rationale as detailed above in Section VII.A.1. for claims 65-90, 94-99, and 101-102. For all of the reasons discussed above in Section VII.A.1., which are incorporated here in their entirety by reference for brevity, Applicant submits that the Examiner has not established a *prima facie* case of unpatentability for claims 114 and 117.

In particular, the Examiner has not established a *prima facie* case of unpatentability for claims 114 and 117 for at least the following reasons. First, the Examiner has failed to establish a *prima facie* case of unpatentability based upon the Ramstack patent for at least the reason that the unsupported assertions form the principal evidence upon which the rejection is based. Second, the unsupported assertions upon which the rejection is based are contrary to the data presented in the '859 application and the explanation provided in the Ramstack Declaration.

Third, independent claim 114 recites a step of "maintaining the microparticles at the conditioning temperature for the time period, wherein an angle of repose of the microparticles at the completion of the maintaining step is less than about 28°" and independent claim 117 recites a step of "maintaining the microparticles at the conditioning temperature for the time period, wherein a flowability index of the microparticles at the completion of the maintaining step is greater than about 60." None of the documents cited by the Examiner discloses or suggests the maintaining steps contained in independent claims 114 and 117, the completion of which is determined by microparticles with an angle of repose of less than about 28° and a flowability index of greater than about 60, respectively. Moreover, none of the documents cited by the Examiner discloses or suggests the claimed angle of repose, its relation to improving flowability of microparticles, and a time period of conditioning of less than about six days and five days, respectively.

B. REJECTION UNDER 35 U.S.C. § 103(a) BASED ON THE CONTI ARTICLE

1. *Claims 65-86, 88-90, 94-99, and 101-102*

Independent claims 65, 80, and 94 (and dependent claims 66-79, 81-86, 88-90, 95-99, and 101-102) have all been rejected under 35 U.S.C. § 103(a) as being unpatentable over the Conti article. The Examiner's reasoning for the Conti article is substantially the same as described above for the Ramstack patent. The Examiner notes the same lack of teaching in the Conti article of the maintaining and conditioning steps of the present invention, and the Examiner makes the same assertions regarding setting aside microparticles to allow them to thoroughly dry, and that increased dryness equals increased flowability. For all of the reasons discussed above in Section VII.A.1., which are incorporated here in their entirety by reference for brevity, Applicant submits that the Examiner has not established a *prima facie* case of unpatentability for claims 65-86, 88-90, 94-99, and 101-102.

In particular, the Examiner has not established a *prima facie* case of unpatentability for claims 65-86, 88-90, 94-99, and 101-102 for at least the following reasons. First, the Examiner has failed to establish a *prima facie* case of unpatentability based upon the Conti article for at least the reason that the unsupported assertions form the principal evidence upon which the rejection is based. Second, the unsupported assertions upon which the rejection is

based are contrary to the data presented in the '859 application and the explanation provided in the Ramstack Declaration. Third, each of independent claims 65 and 80 recites a step of "measuring a flowability index of the conditioned microparticles," and independent claim 94 recites a step of "measuring a flowability index of the hardened microparticles." None of the documents cited by the Examiner discloses or suggests the measuring steps contained in independent claims 65, 80, and 94. Moreover, none of the documents cited by the Examiner discloses or suggests the claimed flowability index or its relation to improving flowability of microparticles.

2. *Claims 103-106, 109-111, 113, and 116*

Independent claims 103, 109, and 116 (and dependent claims 104-106, 110-111, and 113) have all been rejected under 35 U.S.C. § 103(a) as being unpatentable over the Conti article. The Examiner's reasoning for the Conti article is substantially the same as described above for the Ramstack patent. The Examiner notes the same lack of teaching in the Conti article of the maintaining and conditioning steps of the present invention, and the Examiner makes the same assertions regarding setting aside microparticles to allow them to thoroughly dry, and that increased dryness equals increased flowability. For all of the reasons discussed above in Section VII.A.1., which are incorporated here in their entirety by reference for brevity, Applicant submits that the Examiner has not established a *prima facie* case of unpatentability for claims 103-106, 109-111, 113, and 116.

In particular, the Examiner has not established a *prima facie* case of unpatentability for claims 103-106, 109-111, 113, and 116 for at least the following reasons. First, the Examiner has failed to establish a *prima facie* case of unpatentability based upon the Conti article for at least the reason that the unsupported assertions form the principal evidence upon which the rejection is based. Second, the unsupported assertions upon which the rejection is based are contrary to the data presented in the '859 application and the explanation provided in the Ramstack Declaration. Third, each of independent claims 103 and 109 recites a step of "measuring an angle of repose of the microparticles," and independent claim 116 recites a step of "measuring a flowability index of the microparticles." None of the documents cited by the Examiner discloses or suggests the measuring steps contained in independent claims 103, 109,

and 116. Moreover, none of the documents cited by the Examiner discloses or suggests the claimed angle of repose or flowability index, their relation to improving flowability of microparticles, and a time period of conditioning of less than about six days.

3. *Claims 107 and 108*

Independent claims 107 and 108 have both been rejected under 35 U.S.C. § 103(a) as being unpatentable over the Conti article. The Examiner's reasoning for the Conti article is substantially the same as described above for the Ramstack patent. The Examiner notes the same lack of teaching in the Conti article of the maintaining and conditioning steps of the present invention, and the Examiner makes the same assertions regarding setting aside microparticles to allow them to thoroughly dry, and that increased dryness equals increased flowability. For all of the reasons discussed above in Section VII.A.1., which are incorporated here in their entirety by reference for brevity, Applicant submits that the Examiner has not established a *prima facie* case of unpatentability for claims 107 and 108.

In particular, the Examiner has not established a *prima facie* case of unpatentability for claims 107 and 108 for at least the following reasons. First, the Examiner has failed to establish a *prima facie* case of unpatentability based upon the Conti article for at least the reason that the unsupported assertions form the principal evidence upon which the rejection is based. Second, the unsupported assertions upon which the rejection is based are contrary to the data presented in the '859 application and the explanation provided in the Ramstack Declaration. Third, each of independent claims 107 and 108 recites a step of "measuring an angle of repose of the microparticles." None of the documents cited by the Examiner discloses or suggests the measuring steps contained in independent claims 107 and 108. Moreover, none of the documents cited by the Examiner discloses or suggests the claimed angle of repose, its relation to improving flowability of microparticles, and a time period of conditioning of less than about six days.

4. *Claims 114 and 117*

Independent claims 114 and 117 have both been rejected under 35 U.S.C. § 103(a) as being unpatentable over the Conti article. The Examiner's reasoning for the Conti article is

substantially the same as described above for the Ramstack patent. The Examiner notes the same lack of teaching in the Conti article of the maintaining and conditioning steps of the present invention, and the Examiner makes the same assertions regarding setting aside microparticles to allow them to thoroughly dry, and that increased dryness equals increased flowability. For all of the reasons discussed above in Section VII.A.1., which are incorporated here in their entirety by reference for brevity, Applicant submits that the Examiner has not established a *prima facie* case of unpatentability for claims 114 and 117.

In particular, the Examiner has not established a *prima facie* case of unpatentability for claims 114 and 117 for at least the following reasons. First, the Examiner has failed to establish a *prima facie* case of unpatentability based upon the Conti article for at least the reason that the unsupported assertions form the principal evidence upon which the rejection is based. Second, the unsupported assertions upon which the rejection is based are contrary to the data presented in the '859 application and the explanation provided in the Ramstack Declaration. Third, independent claim 114 recites a step of "maintaining the microparticles at the conditioning temperature for the time period, wherein an angle of repose of the microparticles at the completion of the maintaining step is less than about 28°" and independent claim 117 recites a step of "maintaining the microparticles at the conditioning temperature for the time period, wherein a flowability index of the microparticles at the completion of the maintaining step is greater than about 60." None of the documents cited by the Examiner discloses or suggests the maintaining steps contained in independent claims 114 and 117, the completion of which is determined by microparticles with an angle of repose of less than about 28° and a flowability index of greater than about 60, respectively. Moreover, none of the documents cited by the Examiner discloses or suggests the claimed angle of repose, its relation to improving flowability of microparticles, and a time period of conditioning of less than about six days and five days, respectively.

VIII. CLAIMS

A copy of the claims involved in the present appeal is attached hereto as Appendix A. As indicated above, the claims in Appendix A do include the amendments filed by Applicant on March 31, 2004.

IX. EVIDENCE

As noted above, attached hereto as Appendix B is a Declaration of J. Michael Ramstack, Ph.D. Under 37 C.F.R. § 1.132, which is relied upon by the Applicant. The Ramstack Declaration was filed on March 31, 2004, and its entry by the Examiner is evidenced by the Examiner's reference to the Ramstack Declaration on page 7 of the Final Office Action, from which this appeal is taken.

X. RELATED PROCEEDINGS

No related proceedings are referenced in Section II. above. Hence, no Related Proceedings Appendix is needed, and none is included.

XI. CONCLUSION

In view of the above discussion, the Applicant respectfully urges that the rejection of claims 65-90, 94-99, and 101-118 as being unpatentable under 35 U.S.C. § 103(a) is improper. Reversal of the rejections in this appeal is respectfully requested.

Dated: August 19, 2005

Respectfully submitted,

By _____

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APPENDIX A

Claims Involved in the Appeal of Application Serial No. 10/022,859

65. A method for processing microparticles to improve flowability, comprising:

(a) conditioning the microparticles to form conditioned microparticles, wherein the microparticles comprise a polymer selected from the group consisting of poly(glycolic acid), poly-d,l-lactic acid, poly-l-lactic acid, and copolymers of the foregoing;

(b) measuring a flowability index of the conditioned microparticles; and

(c) if the flowability index of the conditioned microparticles is not greater than about 60, repeating step (a) until the flowability index of the conditioned microparticles is greater than about 60.

66. The method of claim 65, wherein step (a) comprises:

(i) maintaining the microparticles at a conditioning temperature for a time period of about five days or less.

67. The method of claim 66, wherein the conditioning temperature is from about 20°C to about 25°C.

68. The method of claim 65, further comprising after step (a):

(b) processing the conditioned microparticles so that the flowability index of the conditioned microparticles is less than about 60.

69. The method of claim 68, wherein step (b) comprises:

(i) tumbling the conditioned microparticles.

70. The method of claim 68, wherein step (b) comprises:

(i) maintaining the conditioned microparticles under vacuum.

71. The method of claim 68, wherein step (b) comprises:

(i) tumbling the conditioned microparticles under vacuum.

72. The method of claim 68, further comprising after step (b):

(c) repeating step (a) so that the flowability index of the conditioned microparticles is greater than about 60.

73. The method of claim 72, wherein step (c) comprises:

(i) maintaining the conditioned microparticles at a conditioning temperature for a time period of about five days or less.

74. The method of claim 73, wherein the conditioning temperature is from about 20°C to about 25°C.

75. The method of claim 65, wherein each of the microparticles comprises an active agent.

76. The method of claim 65, wherein the microparticles comprise microparticles which comprise an active agent.

77. The method of claim 76, wherein the microparticles further comprise placebo microparticles.

78. The method of claim 65, wherein each of the microparticles is a placebo microparticle.

79. The method of claim 65, wherein an angle of repose of the conditioned microparticles is less than about 37°.

80. A method for preparing microparticles having improved flowability, comprising:

(a) preparing an emulsion that comprises a first phase and a second phase, wherein the first phase comprises a polymer selected from the group consisting of poly(glycolic acid), poly-d,l-lactic acid, poly-l-lactic acid, and copolymers of the foregoing, and a solvent for the polymer;

(b) extracting the solvent from the emulsion to form microparticles; and

(c) conditioning the microparticles to form conditioned microparticles;

(d) measuring a flowability index of the conditioned microparticles; and

(e) if the flowability index of the conditioned microparticles is not greater than about 60, then repeating step (c) until the flowability index of the conditioned microparticles is greater than about 60.

81. The method of claim 80, wherein step (b) comprises:

(i) transferring the emulsion to a solvent extraction medium.

82. The method of claim 80, wherein step (c) comprises:

(i) maintaining the microparticles at a conditioning temperature for a time period of about five days or less.

83. The method of claim 82, wherein step (c) is carried out in a temperature-controlled chamber.

84. The method of claim 82, wherein the conditioning temperature is less than a glass transition temperature (T_g) of the polymer.

85. The method of claim 82, wherein the conditioning temperature is from about 20°C to about 25°C.

86. The method of claim 80, wherein the first phase further comprises an active agent.

87. The method of claim 86, wherein the active agent is selected from the group consisting of risperidone, 9-hydroxyrisperidone, and pharmaceutically acceptable salts thereof.

88. The method of claim 87, wherein the solvent comprises benzyl alcohol and ethyl acetate.

89. The method of claim 80, further comprising after step (c):

(d) processing the conditioned microparticles so that the flowability index of the conditioned microparticles is less than about 60.

90. The method of claim 89, further comprising after step (d):

(e) repeating step (c) so that the flowability index of the conditioned microparticles is greater than about 60.

94. A method for preparing microparticles having improved flowability, comprising:

(a) preparing an emulsion that comprises a first phase and a second phase, wherein the first phase comprises a polymer selected from the group consisting of poly(glycolic acid), poly-d,l-lactic acid, poly-l-lactic acid, and copolymers of the foregoing, and a solvent for the polymer;

(b) extracting the solvent from the emulsion to form microparticles; and

(c) hardening the microparticles to form hardened microparticles;

(d) measuring a flowability index of the hardened microparticles; and

(e) if the flowability index of the hardened microparticles is not greater than about 60, then repeating step (c) until the flowability index of the hardened microparticles is greater than about 60.

95. The method of claim 94, wherein step (c) is carried out until a hardness of the hardened microparticles is greater than about 0.4 MPa.

96. The method of claim 94, wherein step (c) comprises:

(i) maintaining the microparticles at a conditioning temperature for a time period of about five days or less.

97. The method of claim 96, wherein the conditioning temperature is less than a glass transition temperature (T_g) of the polymer.

98. The method of claim 96, wherein the conditioning temperature is from about 20°C to about 25°C.

99. The method of claim 94, wherein the first phase further comprises an active agent.

101. The method of claim 65, wherein a hardness of the conditioned microparticles is greater than about 0.4 MPa.

102. The method of claim 80, wherein a hardness of the conditioned microparticles is greater than about 0.4 MPa.

103. A method for processing microparticles to improve flowability, comprising:

(a) selecting a conditioning temperature and a time period for processing the microparticles, wherein the time period is less than about 6 days, and wherein the microparticles comprise a polymer selected from the group consisting of poly(glycolic acid), poly-d,l-lactic acid, poly-l-lactic acid, and copolymers of the foregoing;

(b) maintaining the microparticles at the conditioning temperature for the time period;

(c) measuring an angle of repose of the microparticles;

(d) if the angle of repose of the microparticles is not less than about 28°, adjusting the conditioning temperature and the time period so that the angle of repose of the microparticles is less than about 28°.

104. The method of claim 103, wherein the conditioning temperature is from about 20°C to about 25°C.

105. The method of claim 103, wherein the time period is about two days.

106. The method of claim 103, wherein the time period is about five days.

107. A method for processing microparticles to improve flowability, comprising:

(a) maintaining the microparticles at a conditioning temperature for a time period, wherein the time period is less than about 6 days, and wherein the microparticles

comprise a polymer selected from the group consisting of poly(glycolic acid), poly-d,l-lactic acid, poly-l-lactic acid, and copolymers of the foregoing; and

(b) wherein the conditioning temperature and the time period are determined by

(i) maintaining a portion of the microparticles at the conditioning temperature for the time period,

(ii) measuring an angle of repose of the microparticles, and

(iii) if the angle of repose of the microparticles is not less than about 28°, adjusting the conditioning temperature and the time period and repeating steps (i) and (ii) until the angle of repose of the microparticles is less than about 28°.

108. A method for preparing microparticles having improved flowability, comprising:

(a) preparing an emulsion that comprises a first phase and a second phase, wherein the first phase comprises a polymer selected from the group consisting of poly(glycolic acid), poly-d,l-lactic acid, poly-l-lactic acid, and copolymers of the foregoing, and a solvent for the polymer;

(b) extracting the solvent from the emulsion to form microparticles;

(c) maintaining the microparticles at a conditioning temperature for a time period, wherein the time period is less than about 6 days; and

(d) wherein the conditioning temperature and the time period are determined by

(i) maintaining a portion of the microparticles at the conditioning temperature for the time period,

(ii) measuring an angle of repose of the microparticles, and

(iii) if the angle of repose of the microparticles is not less than about 28°, adjusting the conditioning temperature and the time period and repeating steps (i) and (ii) until the angle of repose of the microparticles is less than about 28°.

109. A method for preparing microparticles having improved flowability, comprising:

(a) preparing an emulsion that comprises a first phase and a second phase, wherein the first phase comprises a polymer selected from the group consisting of poly(glycolic acid), poly-d,l-lactic acid, poly-l-lactic acid, and copolymers of the foregoing, and a solvent for the polymer;

(b) extracting the solvent from the emulsion to form microparticles;

(c) selecting a conditioning temperature and a time period for processing the microparticles, wherein the time period is less than about 6 days;

(d) maintaining the microparticles at the conditioning temperature for the time period;

(e) measuring an angle of repose of the microparticles;

(f) if the angle of repose of the microparticles is not less than about 28°, adjusting the conditioning temperature and the time period so that the angle of repose of the microparticles is less than about 28°.

110. The method of claim 109, wherein the conditioning temperature is less than a glass transition temperature (T_g) of the polymer.

111. The method of claim 109, wherein the conditioning temperature is from about 20°C to about 25°C.

112. The method of claim 109, wherein the active agent is selected from the group consisting of risperidone, 9-hydroxyrisperidone, and pharmaceutically acceptable salts thereof.

113. The method of claim 112, wherein the solvent comprises benzyl alcohol and ethyl acetate.

114. A method for processing microparticles to improve flowability, comprising:

(a) determining a conditioning temperature and a time period for processing the microparticles, wherein the time period is less than about 6 days, and wherein the

microparticles comprise a polymer selected from the group consisting of poly(glycolic acid), poly-d,l-lactic acid, poly-l-lactic acid, and copolymers of the foregoing;

(b) maintaining the microparticles at the conditioning temperature for the time period, wherein an angle of repose of the microparticles at the completion of the maintaining step is less than about 28°.

115. The method of claim 114, wherein the determining step comprises:

(i) measuring an angle of repose of the microparticles;

(ii) if the angle of repose of the microparticles is not less than about 28°, adjusting the conditioning temperature and the time period so that the angle of repose of the microparticles at the completion of the maintaining step is less than about 28°.

116. A method for processing microparticles to improve flowability, comprising:

(a) selecting a conditioning temperature and a time period for processing the microparticles, wherein the time period is less than about 5 days, and wherein the microparticles comprise a polymer selected from the group consisting of poly(glycolic acid), poly-d,l-lactic acid, poly-l-lactic acid, and copolymers of the foregoing;

(b) maintaining the microparticles at the conditioning temperature for the time period;

(c) measuring a flowability index of the microparticles;

(d) if the flowability index of the microparticles is not greater than about 60, adjusting the conditioning temperature and the time period so that the flowability index of the microparticles is greater than about 60.

117. A method for processing microparticles to improve flowability, comprising:

(a) determining a conditioning temperature and a time period for processing the microparticles, wherein the time period is less than about 5 days, and wherein the microparticles comprise a polymer selected from the group consisting of poly(glycolic acid), poly-d,l-lactic acid, poly-l-lactic acid, and copolymers of the foregoing;

(b) maintaining the microparticles at the conditioning temperature for the time period, wherein a flowability index of the microparticles at the completion of the maintaining step is greater than about 60.

118. The method of claim 117, wherein the determining step comprises:

(i) measuring a flowability index of the microparticles;

(ii) if the flowability index of the microparticles is not greater than about 60, adjusting the conditioning temperature and the time period so that the flowability index of the microparticles at the completion of the maintaining step is greater than about 60.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Ramstack *et al.*	Art Unit: 1615
Appl. No.: 10/022,859	Examiner: Amy E. Pulliam
Filed: December 20, 2001	Atty. Docket: 00166.0108.US01
For: **Preparation of Microparticles Having Improved Flowability**	

Declaration of J. Michael Ramstack, Ph.D. Under 37 C.F.R. § 1.132

Commissioner for Patents
Washington, D.C. 20231

I, J. Michael Ramstack, Ph.D., hereby declare and state as follows.

1. I have a B.S. degree in Mechanical Engineering, an M.S. degree in Biomedical Engineering, and a Ph.D. degree in Chemical Engineering. I have over twenty years experience in biotechnology, medical device, and pharmaceutical industries. I am currently employed by Alkermes, Inc. ("Alkermes") as a Senior Development Engineer. I have been employed by Alkermes or their predecessor in business for more than ten years. The above-captioned U.S. Patent Application No. 10/022,859 ("the '859 application") is owned by Alkermes Controlled Therapeutics Inc. II, a subsidiary of Alkermes.

2. I have read and understood the '859 application. I am a co-inventor of the invention disclosed and described in the '859 application.

3. I understand that the Office Action dated December 1, 2003 in the '859 application asserts that "it is within the knowledge of the ordinary artisan that increased dryness equals increased flowability." The data presented in the '859 application are contrary to the assertion that increased dryness equals increased flowability. In particular, Batch E that appears

in Table 3 on page 16 of the '859 application illustrates that increased dryness cannot be equated with increased flowability. As noted in Table 3, the angle of repose of the Batch E placebo microparticles after being in a closed container at room temperature for three years was 19.1°. The Batch E microparticles were then subjected to 24 hours under vacuum, which increased their dryness. After being subjected to further drying under vacuum, the angle of repose increased to 26.5°, a decrease in flowability. The Batch E microparticles demonstrate that increased dryness can lead to decreased flowability.

4. That increased dryness cannot be equated with increased flowability is also demonstrated by Batch F in Table 3 on page 16 of the '859 application. As noted on page 15, lines 16-28 and in Table 3 on page 16 of the '859 application, the Batch F microparticles were conditioned in accordance with the present invention by maintaining them at 25 °C for at least five days. The conditioned Batch F microparticles had an angle of repose of 19.7°. The Batch F microparticles were then subjected to 24 hours under vacuum, which increased their dryness. After being subjected to further drying under vacuum, the angle of repose increased to 24.1°, a decrease in flowability. Like the Batch E microparticles, the Batch F microparticles demonstrate that increased dryness can lead to decreased flowability. Moreover, the Batch F microparticles demonstrate that conditioning the microparticles is not the same as drying microparticles since the conditioned microparticles had better flowability than the microparticles after being further dried under vacuum.

5. On page 8 of the '859 application it is noted that microparticles can be prepared in accordance with, for example, U.S. Patent Nos. 5,650,173 and 5,654,008, and then be subjected to the conditioning process disclosed in the '859 application. I am a co-inventor of the invention

disclosed and described in U.S. Patent No. 5,650,173 ("the '173 patent"). I am familiar with and understand the subject matter of U.S. Patent No. 5,654,008 ("the '008 patent"), which is assigned to Alkermes Controlled Therapeutics Inc. II, through my work at Alkermes. The '173 and '008 patents disclose methods of preparing microparticles in which the microparticles are thoroughly dried. Through my work at Alkermes making microparticles using the methods disclosed in the '173 and '008 patents, it was discovered that the microparticles may exhibit poor flowability, even though the microparticles were thoroughly dried. The process disclosed and described in the '859 application was discovered as a way to improve the flowability of dry but poorly flowing microparticles.

6. I understand that the Office Action dated December 1, 2003 in the '859 application asserts that "it is within the ordinary skill of the pharmaceutical art to set aside a recently made batch of microparticles, allowing them to thoroughly dry, prior to using the microparticles in any further formulations." As explained in paragraph 5 above, even if microparticles are allowed to thoroughly dry, that alone is not a guarantee of good flowability. As explained in paragraphs 3 and 4, increased dryness cannot be equated with increased flowability, and conditioning the microparticles cannot be equated with drying the microparticles.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United

Sates Code and that such willful false statements may jeopardize the validity of the above-captioned patent application or any patent issued thereon.

J Michael Ramstack

J Michael Ramstack

Date: 3-24-04

TRANSMITTAL OF APPEAL BRIEF

Docket No.
000166.0108-US01

In re Application of: J. Michael Ramstack et al.

Application No.	Filing Date	Examiner	Group Art Unit
10/022,859-Conf. #1415	December 20, 2001	S. L. Howard	1615

Invention: PREPARATION OF MICROPARTICLES HAVING IMPROVED FLOWABILITY

TO THE COMMISSIONER OF PATENTS:

Transmitted herewith is the Appeal Brief in this application, with respect to the Notice of Appeal filed: June 21, 2005 .

The fee for filing this Appeal Brief is $ 500.00 .

[x] Large Entity [ ] Small Entity

[ ] A petition for extension of time is also enclosed.

The fee for the extension of time is _____ .

[x] A check in the amount of $ 500.00 is enclosed.

[ ] Charge the amount of the fee to Deposit Account No. _____ .
This sheet is submitted in duplicate.

[ ] Payment by credit card. Form PTO-2038 is attached.

[x] The Director is hereby authorized to charge any additional fees that may be required or credit any overpayment to Deposit Account No. 50-0740 .
This sheet is submitted in duplicate.

Andrea G. Reister

Dated: August 19, 2005

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PTO/SB/17 (12-04v2)
Approved for use through 7/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2005

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 500.00

Complete if Known	
Application Number	10/022,859-Conf. #1415
Filing Date	December 20, 2001
First Named Inventor	J. Michael Ramstack
Examiner Name	S. L. Howard
Art Unit	1615
Attorney Docket No.	000166.0108-US01

METHOD OF PAYMENT (check all that apply)

☒ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☐ Deposit Account Deposit Account Number: 50-0740 Deposit Account Name: Covington & Burling

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☐ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☒ Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17 ☒ Credit any overpayments

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
Application Type	**Fee ($)**	**Small Entity Fee ($)**	**Fee ($)**	**Small Entity Fee ($)**	**Fee ($)**	**Small Entity Fee ($)**	**Fees Paid ($)**
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	**Fee ($)**	**Small Entity Fee ($)**
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	200	100
Multiple dependent claims	360	180

Total Claims	**Extra Claims**	**Fee ($)**	**Fee Paid ($)**
50 - 51 =	_____	x _____	= _____

Multiple Dependent Claims

Fee ($)	**Fee Paid ($)**
_____	_____

Indep. Claims	**Extra Claims**	**Fee ($)**	**Fee Paid ($)**
10 - 10 =	_____	x _____	= _____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	**Extra Sheets**	**Number of each additional 50 or fraction thereof**	**Fee ($)**	**Fee Paid ($)**
_____ - 100 =	_____	/50 _____ (round up to a whole number) x	_____	= _____

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge): 1402 Filing a brief in support of an appeal	500.00

SUBMITTED BY				
Signature	Andrea G. Reister	Registration No. (Attorney/Agent) 36,253	Telephone	(202) 662-6000
Name (Print/Type)	Andrea G. Reister		Date	August 19, 2005